


PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference B6422AA - FP	FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/EP2005/002364	International filing date (day/month/year) 14.02.2005	Priority date (day/month/year) 23.02.2004	
International Patent Classification (IPC) or national classification and IPC INV. G01N30/56			
Applicant BIO-RAD PASTEUR et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 7 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau) a total of 6 sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input checked="" type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 19.12.2005		Date of completion of this report 28.04.2006	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Müller, T Telephone No. +49 89 2399-2285	



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International application No.
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Box No. I Basis of the report

1. With regard to the **language**, this report is based on
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
 - ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))
2. With regard to the **elements*** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

Description, Pages

1, 2, 4-10	as originally filed
3	received on 21.12.2005 with letter of 19.12.2005

Claims, Numbers

1-20	received on 21.12.2005 with letter of 19.12.2005
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Drawings, Sheets

1/2, 2/2	as originally filed
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- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
 - ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing (*specify*):
 - ☐ any table(s) related to sequence listing (*specify*):

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	3-11,16-20
	No: Claims	1,2,12-15
Inventive step (IS)	Yes: Claims	
	No: Claims	1-20
Industrial applicability (IA)	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Reference is made to the following documents:

- D1: EP-A-1 348 957 (BUECHI LAB TECH) 1 October 2003 (2003-10-01)
- D2: PATENT ABSTRACTS OF JAPAN vol. 1996, no. 08, 30 August 1996 (1996-08-30) & JP 08 094603 A (NISSHIN FLOUR MILLING CO LTD), 12 April 1996 (1996-04-12)
- D3: HOFMANN M: "A novel technology for packing and unpacking pilot and production scale columns" JOURNAL OF CHROMATOGRAPHY A, ELSEVIER SCIENCE, NL, vol. 796, no. 1, 13 February 1998 (1998-02-13), pages 75-80, XP004108671 ISSN: 0021-9673
- D4: PATENT ABSTRACTS OF JAPAN vol. 2003, no. 12, 5 December 2003 (2003-12-05) & JP 2004 004093 A (NISSHIN SEIFUN GROUP INC), 8 January 2004 (2004-01-08)
- D5: US-A-5 282 973 (MANN ET AL) 1 February 1994 (1994-02-01)
- D6: DE 39 01 773 A1 (FILTERWERK MANN & HUMMEL GMBH, 7140 LUDWIGSBURG, DE) 26 July 1990 (1990-07-26)
- D7: EP-A-0 150 780 (KLINGER AG) 7 August 1985 (1985-08-07)

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of **claims 1 and 2** is not new in the sense of Article 33(2) PCT.

D1 discloses a method and a device for packing a column with dry resin. D1 discloses a separation column (20) comprising an enclosure (24), a first port (22a), a second port (22b) which is closed with a frit (23a) (see column 5, paragraph [0023]), a tank (11) comprising chromatography resin particles having a size between a minimum and a maximum size, and a pump (14). Particle size is of the order of 10 μm (column 1, line 15) with an average size of 40-65 μm (column 8, lines 2 and 3), the column has any diameter and the wall thickness is typically 1-2 mm (column 5, line 39-40).

Therefore D1 discloses all technical features of present claims 1,2, and corresponding method **claims 12-15**. The wording "a passage having a minimum section which is at least 10000 times as large as a particle section corresponding to the maximum size particles" of claim 1 attempts to define a chromatography column in terms of the filling material, which is not part of the claimed column. A skilled person, having a column with an unknown filling material of small particle diameter would not be able to determine whether the diameter of the used passage would be covered by the subject-matter of the claim or not. As a consequence this wording is unclear and cannot be regarded as a clear structural feature of the column. Applicant argues that D1 does not disclose any numerical value of a column diameter. This argument is not convincing, because claim 1 is also silent on a concrete diameter, stating merely a ratio of particle size and passage.

Furthermore it is noted that document D4 discloses a column diameter of 10 mm and a particle size of 0.15 micrometer (D4, paragraph [0053]) which would present a passage that is about 10000 times larger than the particle size.

The subject-matter of **claim 3** differs from D1 in that an inlet valve is provided. This solution proposed in claim 3 of the present application cannot be considered as involving an inventive-step (Article 33(3) PCT), because a skilled person would combine the teaching of D2 which discloses inlet valve (14).

Method **claims 16-20** are related to unloading a chromatography resin mixed with a liquid.

Insofar the claim can be understood at present (see VIII below), the subject-matter of claims 16-20 seems to be not inventive over the disclosure of D3 or D4, where chromatography columns are unloaded. Although not mentioned explicitly, the choice of a large diameter for the discharge of the column and drying of the particles before the discharge seems straightforward (Article 33(3) PCT).

The subject-matter of **claim 4** does not meet the requirements of inventive step (Article 33(3) PCT), the reasons being as follows:

Document D1 discloses a method and a device for packing a column with dry resin comprising a separation column (20), an enclosure (24), a first port (22a), a second port

(22b) which is closed with a frit (23a) (see column 5, paragraph 23), a tank (11) comprising chromatography resin particles having a size between a minimum and a maximum size, and a pump (14).

As a consequence, the features enclosure, first port, and second port of independent claim 4 are known from document D1, and claim 4 differs from D1 in an inlet valve comprising chamber, inlet duct and piston. The general concept of an inlet valve for charge and discharge of a column is known from D2 or D5, and details of the arrangement of piston, chamber and ducts are well established in the field of transport of granular material, see for example D6 or D7.

The subject-matter of dependent **claims 5 - 9** is related to details which a skilled person would employ according to the circumstances, without inventive activity (Article 33(3) PCT).

The arrangement of column, pump and pipe is known from D1, see figure 6, and a combination with a valve as in D6 or D7 would be straightforward. The subject-matter of **claims 10 and 11** is therefore also not inventive over the prior art as disclosed in the search report (Article 33(3) PCT).

Re Item VIII

Certain observations on the international application

The application lacks clarity (Article 6 PCT), the reasons being as follows:

Claim 1 is not clear in that the wording of the claim leads to a doubt whether a pump (5) is part of the claimed device or not.

The wording "a passage having a minimum section which is at least 10000 times as large as a particle section corresponding to the maximum size particles" of claims 1, 12, and 16 attempts to define a chromatography column in terms of the filling material, which is not part of the claimed column. A skilled person, having a column with an unknown filling material of small particle diameter would not be able to determine whether the diameter of the used passage would be covered by the subject-matter of the claim or not. As a

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consequence this wording is unclear.

Claim 7 seems to comprise a repetition of the features of claim 1.

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from a chromatography column ~~into a chromatography column~~ comprising an enclosure, a first port, to put the enclosure in communication with a tank comprising chromatography resin particles having a size distributed between a minimum size and a maximum size, and a second port, to put the enclosure in communication with a pump, wherein the first port forms a passage having a minimum section which is at least 10 000 times as large as a particle section corresponding to the maximum size particles.

10 Embodiments of such an unloading method may include one or more of the following features. The column comprises an enclosure having a high port located above a low port, this method comprises successively the steps of a) pumping the liquid from the enclosure through the low port,
15 b) drying the chromatography resin comprised in the enclosure, and c) pumping the dried resin through the low port. The vacuum pressure in the enclosure is between -100 kPa and -50 kPa. The unloading method according to the invention further comprises between steps b) and c),
20 injecting a gas through the low port. Step b) of this method comprises injecting a hot gas through the low port in order to totally dry the resin. Step b) may also comprise injecting a hot gas through the high port. The hot gas can be steam, even if steam is not used in 100 % of the
25 unloading cases.

Another aspect of the invention provides a chromatography column comprising an enclosure and a first port. The first port puts the enclosure in communication with a tank comprising chromatography resin particles
30 having a size distributed between a minimum size and a maximum size (these minimum and maximum can be for example respectively 10 μm and 300 μm , but most common sizes are comprised between 40 and 80 μm ; of course the pore size of column filters is adapted to the particle size) This
35 chromatography column also comprises a second port. The

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CLAIMS

1.A chromatography column comprising an enclosure (9), a first port (33), suitable to put the enclosure (9) in communication with a tank (7) comprising chromatography resin particles having a size distributed between a minimum size and a maximum size, and a second port (35), suitable to put the enclosure (9) in communication with a pump (5), wherein the first port (33) forms a passage having a minimum section which is at least 10 000 times as large as a particle section corresponding to the maximum size particles.

2. The chromatography column of claim 1, wherein the enclosure (9), when in use, extends vertically between a bottom (11) and a top (13), the second port (35) being located above the first port (33).

3. The chromatography column of any of the preceding claims, wherein the first port (33) is provided with an inlet valve (39) having a minimum section which is at least 10 000 times as large as the particle section corresponding to the maximum size particles.

4. A chromatography column according to any one of claim 1-3, characterized in that:

said first port (33) is provided with an inlet valve (39), suitable to put the enclosure (9) in communication with a tank (7) comprising chromatography resin particles having a size distributed between a minimum size and a maximum size, and

wherein the inlet valve (39) comprises a chamber (41), an inlet duct (43) and a piston (45),

- the chamber (41) communicating with the enclosure

(9) through a first aperture (47),

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- the inlet duct (43) communicating with the chamber (41) through a second aperture (49) and being adapted to be connected to the tank (7), and
- the piston (45) being movable in the chamber (41) between a closing position, where it closes the first (47) and second (49) apertures, and an opening position, where it opens the first (47) and second (49) apertures, said piston (45) letting free substantially all the space of the chamber (41) between the first (47) and second (49) apertures.

5. The chromatography column of claim 4, wherein the enclosure (9), when in use, extends vertically between a bottom (11) and a top (13), the second port (35) being located above the first port (33).

6. The chromatography column of claim 4 or claim 5, wherein the valve (39) defines a passage between a pipe (51) adapted to be connected to the duct (43) and the enclosure (9), said passage having a minimum section which corresponds to the section of any of the first (47) and second (49) apertures.

7. The chromatography column of claim 6, wherein the minimum section of the passage is at least 10 000 times as large as the particle section corresponding to the maximum size particles.

8. The chromatography column according to any of claims 4 to 7, wherein the piston (45) when in closing position has an end surface (53) with a tapered shape, said end surface having a portion which is flush with the internal surface of the enclosure (9).

9. The chromatography column of any of the

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preceding claims, wherein the first port (33) forms a passage having a minimum section corresponding to at least a minimum internal diameter of 20 mm.

5 10. A module for loading a chromatography resin into a chromatography column (3) according to any of the preceding claims, said module (1) comprising said chromatography column (3) and a pump (5) connected to the second port (35) through a pipe (40).

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11. The module according to claim 10, further comprising a tank (7) for chromatography resin, said tank (7) being connected to the first port (33).

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12. A method for loading a chromatography resin into a chromatography column (3) comprising an enclosure (9), a first port (33), suitable to put the enclosure (9) in communication with a tank (7) comprising chromatography resin particles having a size distributed between a minimum size and a maximum size, and a second port (35), suitable to put the enclosure (9) in communication with a pump (5), wherein the first port (33) forms a passage having a minimum section which is at least 10 000 times as large as a particle section corresponding to the maximum size particles.

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13. A method according to claim 12, wherein said column (3) comprises an enclosure (9) having a first port (33) and a second port (35), and said method comprising pumping a dry chromatography resin from a resin tank (7) into the enclosure (9) through the first port (33), via a pump (5) connected to a second port (35).

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14. The method of claim 12 or claim 13, wherein the vacuum pressure in the enclosure is between -100 kPa and -

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50 kpa.

15. The method according to any of claim 12 to claim 14, wherein the enclosure (9), when in use, extends vertically between a bottom (19) and a top (13), the second part (35) being located above the first port (33).

16. A method for unloading a chromatography resin mixed with a liquid, from a chromatography column (3) comprising an enclosure (9), a first port (33), suitable to put the enclosure (9) in communication with a tank (7) comprising chromatography resin particles having a size distributed between a minimum size and a maximum size, and a second port (35), suitable to put the enclosure (9) in communication with a pump (5), wherein the first port (33) forms a passage having a minimum section which is at least 10 000 times as large as a particle section corresponding to the maximum size particles.

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17. The method of claim 16, wherein said column comprises an enclosure (9) having a high port (35) located above a low port (33 or 37), this method comprising successively the steps of

- 25 - a) pumping the liquid from the enclosure through the low port (33 or 37),
 - b) drying the chromatography resin comprised in the enclosure (9), and
 - c) pumping the dried resin through the low part
30 (33 or 37).

18. The method according to any of claims 16 and 17, wherein the vacuum pressure in the enclosure (9) is between -100 kPa and -50 kPa.

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19. The method according to any of claims 17 and 18, further comprising between steps b) and c) injecting a gas through the low port (33 or 37).

5 20. The method according to any of claims 17 to 19, in which step b) comprises injecting a hot gas through the high port (35).